IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Berndl et al.	Docket No.:	49860
Application No.:	09/937,313	Examiner:	YOUNG
Filed:	9/24/2001	Art Unit:	1618
Customer No.:	26474	Confirmation No.:	8414

For: Solubilizing aids in powder form for solid pharmaceutical presentation forms

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Sir:

This is an appeal from the final rejection mailed May 28, 2008. The fee of $540.00 set forth in 37 C.F.R. § 41.20(b)(2) is paid by credit card.

Appellants request a one-month extension of time; the fee of $130.00 is paid by credit card. Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit Account 14.1437. Please credit any excess fees to such account.

REAL PARTY IN INTEREST:

The real party in interest is BASF SE, of Ludwigshafen, Germany.

RELATED APPEALS AND INTERFERENCES:

To the best of the undersigned's knowledge, there are no related interferences or judicial proceedings.

STATUS OF CLAIMS:

Claims 10 – 12, 14 – 18, and 20 – 24 are pending. Claims 10 – 12, 14 – 18, and 20 – 24 stand rejected. Claims 10 – 12, 14 – 18, and 20 – 24 are being appealed. Claims 1 – 9, 13, 19, and 25 – 28 are canceled. No claims are objected to, allowed, or confirmed. No claims are subject to an election/restriction requirement. No claims have been withdrawn from consideration.

STATUS OF AMENDMENT:

No amendment to the claims or to the specification was filed subsequent to the above-identified final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER:

Independent claim 10 relates to a process for producing an excipient adapted for use in a solid pharmaceutical dosage form.[1] The process comprises either spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer,[2] or processing the polymer and the surface-active substance in an extruder to

[1] Specification, page 1, lines 1 – 2.
[2] Specification, page 3, lines 31 – 37.

obtain a homogeneous melt[3] and subsequently converting the melt into the free-flowing powder.[4] The excipient produced by the process must be in the form of a free-flowing powder.[5] The excipient must consist essentially of a pharmaceutically acceptable polymer, and from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance.[6] The polymer must be a homo- or copolymer of N-vinylpyrrolidone.[7] The polymer must be a water-soluble polymer.[8] The polymer must have Fikentscher K values of from 12 to 100.[9] The liquid or semisolid solubilizing surface-active substance must comprise ethoxylated sorbitan fatty acid esters, or the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid.[10]

Claim 11 relates to the process according to claim 10, wherein the excipient comprises a surface-active substance which has a drop point in the range from 20 to 40°C.[11]

Claim 12 relates to the process according to claim 10, wherein the excipient comprises a surface-active substance which has an HLB of from 10 to 15.[12]

Claim 14 relates to the process according to claim 10, wherein the excipient comprises from 15 to 40% by weight of the surface-active substance.[13]

Claim 15 relates to the process according to claim 10, wherein the excipient comprises ethoxylated sorbitan fatty acid esters as surface-active substances.[14]

Claim 16 relates to the process according to claim 10, wherein the excipient comprises the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface active substance.[15]

Claim 17 relates to the process according to claim 10, wherein the excipient

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[3] Specification, page 3, line 44 – page 4, line 2, and Example 2.
[4] Specification, page 4, lines 4 – 11, lines 20 – 21, and Example 2.
[5] Specification, page 4, lines 20 – 21.
[6] Specification, page 2, lines 9 – 14.
[7] Specification, page 3, lines 15 – 21.
[8] Specification, page 3, lines 15 – 21.
[9] Specification, page 3, lines 15 – 21.
[10] Specification, page 3, lines 4 – 10.
[11] Specification, page 2, lines 16 – 21.
[12] Specification, page 2, lines 16 – 21.
[13] Specification, page 2, lines 9 – 14.
[14] Specification, page 2, lines 36 – 45.
[15] Specification, page 3, lines 4 – 10.

comprises from 20 to 30% by weight of the surface-active substances.[16]

Claim 18 relates to the process according to claim 10, wherein the excipient is in the form of a free-flowing powder of particles having a particle size of from 10 to 1000 μ.[17]

Claim 20 relates to the process according to claim 10, wherein the surface-active substance of the excipient is a non-ionic compound.[18]

Claim 21 relates to the process of claim 10, wherein said excipient is free of pigment.[19]

Independent claim 22 relates to a process for producing a free-flowing powder excipient for use in a solid pharmaceutical dosage form.[20] The process comprises producing the free-flowing powder excipient by one of: spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer,[21] or extruding the polymer and the surface-active substance to obtain a homogeneous melt[22] and subsequently converting the melt into the free-flowing powder.[23] The free-flowing powder excipient produced according to the process must consist essentially of a pharmaceutically acceptable polymer, and from 10 to 50% by weight, based on the total weight of the excipient, of a liquid or semisolid solubilizing surface-active substance.[24] The pharmaceutically acceptable polymer in the excipient must be a homo- or copolymer of N-vinylpyrrolidone.[25] The pharmaceutically acceptable polymer in the excipient must be a water-soluble polymer.[26] The pharmaceutically acceptable polymer in the excipient must have Fikentscher K values of from 12 to 100.[27] The surface active substance must be in a suitable concentration to keep the excipient free flowing.[28]

Claim 23 relates to the process of claim 22, wherein the concentration of surface

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[16] Specification, page 2, lines 9 – 14.
[17] Specification, page 4, lines 20 – 21.
[18] Specification, page 2, lines 23 – 24.
[19] Specification, page 2, lines 9 – 14.
[20] Specification, page 1, lines 1 – 2.
[21] Specification, page 3, lines 31 – 37.
[22] Specification, page 3, line 44 – page 4, line 2, and Example 2.
[23] Specification, page 4, lines 4 – 11, lines 20 – 21, and Example 2.
[24] Specification, page 2, lines 9 – 14.
[25] Specification, page 3, lines 15 – 21.
[26] Specification, page 3, lines 15 – 21.
[27] Specification, page 3, lines 15 – 21.
[28] Specification, page 4, lines 20 – 21.

active substance is 15 to 40% by weight based on the weight of the excipient.[29]

Claim 24 relates to the process of claim 22, wherein the concentration of surface active substance is 20 to 30% by weight based on the weight of the excipient.[30]

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:

I. Claims 10 – 12, 14 – 18, 20 and 22 – 24 stand rejected in view of: 35 U.S.C §103(a), US 4,127,422 to Guzi Jr. et al. (hereinafter, "Guzi"), US 5,858,412 to Staniforth et al. (hereinafter, "Staniforth"), and US 6,086,915 to Zeligs et al. (hereinafter, "Zeligs").
II. Claims 10, 15, 16, 18, 20 and 21 stand rejected in view of: 35 U.S.C §103(a), US 6,066,334 to Kolter et al. (hereinafter, "Kolter"), Staniforth, and Zeligs.

ARGUMENT:

I. Claims 10 – 12, 14 – 18, 20, and 22 – 24 stand rejected in view of 35 U.S.C §103(a), Guzi, Staniforth, and Zeligs.

Appellants respectfully request review of whether all of the elements claimed in claims 10 – 12, 14 – 18, 20, and 22 – 24 were known in Guzi, Staniforth, and Zeligs, whether one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and whether the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

As expressed by the U.S. Supreme Court, "[t]he rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded

[29] Specification, page 2, lines 9 – 14.
[30] Specification, page 2, lines 9 – 14

nothing more than predictable results to one of ordinary skill in the art."[31] Furthermore, "[t]he determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[32]

A) Spray-drying a solution

The processes according to independent claims 10 and 22 require spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable polymer, or processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder. The Office action does not allege that it would have been obvious to process the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently convert the melt into the free-flowing powder.

i. Appellants respectfully request review of whether spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable polymer was known in Guzi, Staniforth, and Zeligs.

Guzi spray-dries a dispersion to obtain a pigment composition, having a high concentration of pigment. The dispersion that is spray-dried according to Guzi must comprise milled or homogenized pigment, water, a non-ionic dispersing agent, and a water-dispersible non-ionic polymer. As expressed in column 3, lines 44 – 46, Guzi goes to great lengths simply to disperse the all-important pigment particles, and provides no indication that it would even be possible to produce a solution comprising the pigment. Thus, contrary to the perfunctory statement on page 2 of the final Office action mailed May 28, 2008, Guzi does not disclose spray-drying a solution.

In columns 13 and 14, Staniforth describes a method for preparing a

[31] MPEP §2143, citing *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950) (emphasis added).

[32] *Sanofi-Synthelabo, Inc. v. Apotex, Inc.* Fed. Cir. 2007-1438 (2008), citing KSR Int'l Co. v. Teleflex, Inc. 127 S.Ct. 1727, 1734 (2007); and *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984).

microcrystalline cellulose excipient by spray-drying an aqueous dispersion comprising microcrystalline cellulose and surfactant. According to column 13, lines 6 – 13, a well-dispersed aqueous slurry of microcrystalline cellulose in which a compressibility augmenting agent has been dissolved, is formed and subsequently dried to form a plurality of microcrystalline cellulose-based excipient particles. As stated in column 13, lines 22 – 25, the suspension must be kept under constant agitation for a sufficient time to assure a uniform distribution of the solids prior to being combined with the compressibility augmenting agent. Furthermore, column 13, lines 31 – 33 of Staniforth explain that there is no appreciable dissolution of either ingredient (microcrystalline cellulose or silicon dioxide), since both are relatively water insoluble. Thus, applicants respectfully submit Staniforth does not describe or suggest spray-drying a solution.

Zeligs relates to nutrient preparations and formulation techniques using plant-based compounds. According to column 10, lines 5 – 8, new formulation technology was developed which permits the creation of a microdispersion of insoluble dietary substances in association with polyethylene glycol esters and natural surfactants. At column 10, lines 9 – 10, Zeligs goes on to explain, this microdispersion is captured within particles of starch through a spray-drying process. Thus, Zeligs does not describe or suggest spray-drying a solution.

Appellants respectfully submit that Guzi, Staniforth, and Zeligs do not describe or even suggest spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable polymer. The references do not describe spray-drying a solution at all.

ii. Appellants also respectfully request review of whether one skilled in the art could have combined the elements described in Guzi, Staniforth, and Zeligs by known methods with no change in their respective functions to arrive at the present invention.

The final Office action mailed May 28, 2008 does not rely on Staniforth, or Zeligs to provide an apparent reason to spray-dry a solution. Instead, the Office action alleges, one of ordinary skill in the art would have been motivated to combine the surfactants of

Staniforth and Zeligs to provide improved stability and compressibility of the microparticles resulting from the spray-drying process of Guzi.

As discussed above, however, Guzi does not disclose spray-drying a solution. No evidence of record suggests that adding the Staniforth and Zeligs surfactants to the Guzi dispersion would result in the dissolution of the Guzi pigment particles. Furthermore, a person of ordinary skill in the art had no apparent reason to omit the pigment particles from the Guzi dispersion, because doing so would render the Guzi process unsatisfactory for its intended purpose of producing a dry pigment composition containing 55 to 80 % pigment.

Appellants respectfully submit, therefore, that Guzi, Staniforth and Zeligs cannot be combined to result in a process comprising spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable carrier.

iii. Finally, appellants respectfully request review of whether the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

As discussed above, the proposed combination would not have resulted in the present invention. Appellants respectfully submit, however, that the present invention yields results that were not predictable at the time the invention was made. As expressed on page 1, line 44 – page 2, line 2 of the specification, at the time the invention was made, using the solubilizing surface-active substances employed in claim 10, in the amounts employed in claims 10 and 22 would have been expected to yield a formulation having a waxy consistency and processability problems. According to the present invention a procedure which permits larger amounts of liquid or semisolid solubilizing surface-active substances to be employed was unexpectedly discovered.

B) An excipient for use in a solid pharmaceutical dosage form.

The processes according to independent claims 10 and 22 produce an excipient for use in a solid pharmaceutical dosage form.

i. Appellants respectfully request review of whether an excipient for use in a solid pharmaceutical dosage form was known in Guzi, Staniforth, and Zeligs.

The Office action proposes modifying the Guzi excipient based on Staniforth and Zeligs, and does not propose utilizing any excipient described in either Staniforth or Zeligs. As expressed in column 1, lines 49 – 68, Guzi relates to dry, water-dispersible compositions having broad compatibility in latex and other aqueous systems, such as paper coating compositions, disposable nonwovens, melamine-formaldehyde laminates, ink systems and universal colorant systems. Guzi does suggest that its excipient would be useful in a solid pharmaceutical dosage form.

ii. Appellants also respectfully request review of whether one skilled in the art could have combined the elements described in Guzi, Staniforth, and Zeligs by known methods with no change in their respective functions to arrive at an excipient for use in a solid pharmaceutical dosage form.

Without the benefit of the present application to provide a blueprint for a hindsight reconstruction, Appellants respectfully submit that a skilled artisan could not have combined the Guzi pigment composition with the surfactants of Staniforth and Zeligs to arrive at an excipient for use in a solid pharmaceutical dosage form. No apparent reason existed to do so. No design need or market pressure would have prompted the proposed combination. Moreover, a skilled artisan had no apparent reason to assume that the pigments employed in the Guzi pigment compositions – intended primarily for use in commercial latex paints – would be suitable for use in a solid pharmaceutical dosage form.

C) Excipient consisting essentially of a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

The process according to independent claim 10 produces an excipient that consists essentially of a pharmaceutically acceptable polymer, wherein the polymer is a

homo- or copolymer of N-vinylpyrrolidone, which is a water-soluble polymer with Fikentscher K values of from 12 to 100, and from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance, comprising ethoxylated sorbitan fatty acid esters, or the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid.

The process according to independent claim 22 produces an identical excipient, except that the liquid or semisolid solubilizing surface-active substance must be present in a suitable concentration to keep the excipient free flowing, and need not comprise ethoxylated sorbitan fatty acid esters, or the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid.

"The transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention."[33] The Advisory Action of November 17, 2008, misconstrues the law, stating, "the language consisting essentially [of] only removes components that fundamentally change the resulting composition. The composition of the '422 patent remains an excipient, within the same field of endeavor as the instant claims."[34]

Applicants respectfully submit high amounts (from 55 to 80 wt %) of solid pigment particles, as required by Guzi, are excluded by the transitional phrase "consisting essentially of," because their presence would affect the basic and novel characteristics of the claimed invention. It is a basic and novel characteristic of the present invention that the claimed process produces an excipient for use in a solid pharmaceutical dosage form. As discussed above, a skilled artisan had no apparent reason to assume the pigments employed in the Guzi pigment compositions, which were intended primarily for use in commercial latex paints, would be suitable for use in a solid pharmaceutical dosage form.

II. Claims 10, 15, 16, 18, 20 and 21 stand rejected in view of 35 U.S.C §103(a), Kolter, Staniforth, and Zeligs.

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[33] MPEP §2111.03, citing *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis added).

[34] Page 2, lines 5 – 7 of the Advisory action mailed November 17, 2008 (emphasis added).

The processes according to independent claims 10 and 22 require spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable polymer, or processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder. The Office action does not allege that it would have been obvious to process the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently convert the melt into the free-flowing powder.

i. Appellants respectfully request review of whether spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable polymer was known in Kolter, Staniforth, and Zeligs.

Kolter relates to the use of redispersible polymer powders or polymer granules consisting of polyvinyl acetate and N-vinylpyrrolidone-containing polymers as binders for producing pharmaceutical presentations. At column 2, lines 63 – 67, Kolter explains, the redispersible polymer powders are produced by initial emulsion polymerization of vinyl acetate, then addition of the N-vinylpyrrolidone-containing polymer, with or without other ancillary substances, to the resulting shear-stable and fine-particle dispersion, and spray-drying of the mixture. Thus, Kolter describes spray drying a fine-particle dispersion not a solution. In fact, at column 2, lines 52 – 53, Kolter explains, polyvinyl acetate is insoluble in water.

As discussed above, Staniforth and Zeligs do not describe or suggest spray-drying a solution.

ii. Appellants also respectfully request review of whether one skilled in the art could have combined the elements described in Kolter, Staniforth, and Zeligs by known methods with no change in their respective functions to arrive at the present invention.

The final Office action mailed May 28, 2008 does not rely on Staniforth, or Zeligs to provide an apparent reason to spray-dry a solution. Instead, the Office action alleges,

one of ordinary skill in the art would have been motivated to combine the surfactants of Staniforth and Zeligs to provide improved stability and compressibility of the particles produced by the spray-drying process of Kolter.

As discussed above, however, Kolter does not disclose spray-drying a solution. No evidence of record suggests that adding the Staniforth and Zeligs surfactants to the Kolter dispersion would result in the dissolution of polyvinyl acetate. Furthermore, a person of ordinary skill in the art had no apparent reason to omit polyvinyl acetate from the Kolter dispersion, because doing so would render the Kolter process unsatisfactory for its intended purpose of producing redispersible polymer powders or polymer granules consisting of 10 – 95% by weight of polyvinyl acetate.

Appellants respectfully submit, therefore, that Kolter, Staniforth and Zeligs cannot be combined to result in a process comprising spray-drying a solution comprising a surface-active substance and a pharmaceutically acceptable carrier.

iii. Finally, appellants respectfully request review of whether the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

Again, the proposed combination of Kolter, Staniforth, and Zeligs would not have resulted in the present invention. Moreover, as discussed above, the present invention yields results that were not predictable at the time the invention was made. According to the present invention a procedure which permits larger amounts of liquid or semisolid solubilizing surface-active substances to be employed was unexpectedly discovered.

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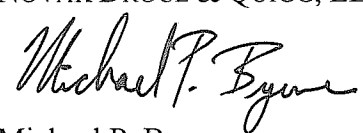

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CLAIMS APPENDIX:

1. – 9. (canceled).

10. (currently amended) A process for producing an excipient adapted for use in a solid pharmaceutical dosage form, wherein said excipient is in the form of a free-flowing powder and consists essentially of:

a pharmaceutically acceptable polymer, wherein the polymer is a homo- or copolymer of N-vinylpyrrolidone, which is a water-soluble polymer with Fikentscher K values of from 12 to 100, and

from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance, comprising ethoxylated sorbitan fatty acid esters, or the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid,

said process comprising either:

spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer, or

processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder.

11. (previously presented) The process according to claim 10, wherein the excipient comprises a surface-active substance which has a drop point in the range from 20 to 40°C.

12. (previously presented) The process according to claim 10, wherein the excipient comprises a surface-active substance which has an HLB of from 10 to 15.

13. (canceled)

14. (previously presented) The process according to claim 10, wherein the excipient comprises from 15 to 40% by weight of the surface-active substance.

15. (previously presented) The process according to claim 10, wherein the excipient comprises ethoxylated sorbitan fatty acid esters as surface-active substances.

16. (previously presented) The process according to claim 10, wherein the excipient comprises the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface active substance.

17. (previously presented) The process according to claim 10, wherein the excipient comprises from 20 to 30% by weight of the surface-active substances.

18. (previously presented) The process according to claim 10, wherein the excipient is in the form of a free-flowing powder of particles having a particle size of from 10 to 1000 μ.

19. (canceled)

20. (previously presented) The process according to claim 10, wherein the surface-active substance of the excipient is a non-ionic compound.

21. (previously presented) The process of claim 10, wherein said excipient is free of pigment.

22. (currently amended) A process for producing a free-flowing powder excipient for use in a solid pharmaceutical dosage form consisting essentially of:

a pharmaceutically acceptable polymer, and

from 10 to 50% by weight, based on the total weight of the excipient, of a liquid or semisolid solubilizing surface-active substance, wherein

the pharmaceutically acceptable polymer in the excipient is a homo- or copolymer of N-vinylpyrrolidone, and

is a water-soluble polymer with Fikentscher K values of from 12 to 100

the process comprising producing the free-flowing powder excipient by one of:

spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer, or

extruding the polymer and the surface-active substance to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder, wherein

the surface active substance is in a suitable concentration to keep the excipient free flowing.

23. (previously presented) The process of claim 22, wherein the concentration of surface active substance is 15 to 40% by weight based on the weight of the excipient.

24. (previously presented) The process of claim 22, wherein the concentration of surface active substance is 20 to 30% by weight based on the weight of the excipient.

25 – 28. (canceled)

EVIDENCE APPENDIX:

None.

RELATED PROCEEDINGS APPENDIX:

None.